

CHALLENGE OF TRANSPLANTATION

Thank you for the opportunity to give this talk.

The first whole organ transplant between unrelated individuals which was considered a success took place in 1962. That year my teacher suggested that I take a fellowship in immunology to prepare myself to study the field.

My first cadaver donor transplant was done in the autumn of 1964. I was still an immunology fellow, and we as an institution were not properly prepared to undertake our first clinical transplant, but a man was admitted in uremic coma. By chance, a young man with a lethal head injury was also in our intensive care unit whose family agreed to donation. I shall never forget the emotional difficulty I had in approaching this family. That responsibility was then and has forever after been distasteful to me. We had several renown nephrologists in our institution, but none were interested in chronic dialysis. The Department of Medicine had a second or third generation artificial kidney and a box of dialysis coils locked in a storeroom under a dusty tarpaulin. I could get no help from nephrology. A friend and I broke into the storeroom and stole the dialyzer. We spent several

hours figuring out how to make it run. We put a scribner plastic shunt in place and dialyzed the patient for several hours. We knew nothing about disequilibrium syndrome, but probably the dialyzer was too inefficient to produce it. The patient went from coma to stupor, but his numbers improved. The patient and donor were taken to a recovery area. Several of us stood by at the bedside watching the EKG. When the EKG went flat we scrambled to the operating room and removed the kidneys in a very rapid way. A technique that would have appalled Halsted. Meantime, the recipient was being prepared in the next room. The kidney was washed out with heparinized saline and submerged in cold saline. This kidney functioned immediately, but the patient died about two weeks later of pneumonia. A few weeks later, however, another graft was done and that patient survived many years. I was chastised by the chairman of medicine for irresponsibility, but fortunately my chief protected me. It has been said that all progress is made by unreasonable people, an aphorism which has become less agreeable to me as I have grown older, but I did learn that it is commonly necessary for older chiefs to be patient with younger alturistic surgeons. I describe this episode to illustrate how primitive

these early efforts were in contrast with today, as well as to illustrate that the entire field of human clinical transplantation has developed within one professional lifetime. The field has gone from science fiction to clinical reality in 33 years.

The challenge of transplantation seems to me to involve two separate issues. The first is science. The second involves ethics. I will discuss these two separately.

SCIENCE

Almost all medical progress is based upon many contributions which lay a foundation before a breakthrough occurs and transplantation is no exception. I will only discuss four, although there were many others.

SLIDE 1

Wilhelm Kolff was a Dutch Jew who was a physician in a small town in the Netherlands during World War II. Many patients injured in that war developed acute renal failure - variously described as lower nephron nephroses or crush syndrome. Professor Kolff was called upon to treat such patients. He learned that if he could keep the patient alive for 15-20 days the kidneys would recover. He set about designing a dialysis machine or artificial kidney to

prolong survival long enough for natural recovery to take place. He struggled with containers, membranes and pumps. He finally obtained a usable prototype near the war's end. He tried his machines on 15 patients between 1943-1945 and only one patient survived. Professor Kolff was not unmindful of the Nazi treatment of Jews. He also realized that the Germans were watching his research with great interest since success would lead to the salvage of many German lives. I heard Professor Kopff relate his efforts in a lecture given many years after the war. In this talk he implied that he was not too anxious to produce the ideal dialyzer because he feared he would be killed by the Nazi's as soon as they had the machine and thus no longer needed him. By war's end he had four prototypes. One he took to Oxford, one to Boston, and one to Russia.

This artificial kidney was soon used around the world. It was improved and shortly was applied to patients with chronic renal failure as well as acute renal failure. Thus a pool of patients accumulated who were alive with chronic renal failure condemned to repeated dialysis which maintained life, but although patients survived, they did not thrive and were chronically debilitated.

Fortunately through previous animal work a technique for transplanting kidneys in dogs had been devised. This was a brilliantly conceived and relatively simple operation which is performed today almost precisely as it was worked out in the early 50's.

Great technical advantages of the kidney transplant procedure were that the organ was placed extraperitoneal and at the brim of the pelvis. If the kidney failed for some reason there was no intraperitoneal complication such as peritonitis. It was much simpler to place the kidney in the iliac fossa and the ureter could be greatly shortened, which prevented ischemic necrosis at the distal end.

By 1954 a patient presented at the Peter Bent Brigham Hospital with chronic renal failure who had an identical twin. Previous work had indicated that skin grafts between identical twins survived, but no one knew about whole organs - what would be the effect of denervating the organ? Would the hormones produced by the kidney still be properly controlled? What about the effects on blood pressure and volume control?

Thus, the scene was set and the first successful human whole

organ transplant was done between identical twins in 1954. This patient's new kidney performed perfectly. Subsequently a few dozen other identical twin transplants were performed. This experiment proved there was no barrier to organ transplantation other than the immune response.

The fourth foundation was the discovery of a drug to suppress the immune response. This did not come about until 1960 with the discovery of azathioprine, although some efforts to use total body irradiation in the intervening years were largely unsuccessful.

These four innovations led to attempts at renal transplantation between unrelated individuals. The third such attempt using azathioprine led to survival longer than one year and is considered the first successful transplant of its type. This transplant was done in 1962.

SLIDE 2 -Kolff

SLIDE 3 - Murray

Shortly afterward cortisone was recognized as an effective immunosuppressant (1963). Antilymphocyte globulin was first used (reported) in 1966.

For 17 years thereafter the fundamental treatment for control

of rejection was Imuran, Prednisone, and Antilymphocyte globulin.

Initial attempts at heart transplants began in 1967 and liver transplants started in 1968. These attempts broke new ground, established appropriate technology, and defined special problems, but were largely unsuccessful until 1983 when Cyclosporine was introduced.

There was gradual improvement in the safety, reliability, and long term results through these 17 years. Almost all of this progress reflected broader experience with attention to details.

SLIDE 4

There were other advances in immunobiology. Blood groups were recognized as histocompatibility antigens and the human leukocyte antigens were uncovered. A long series of studies by many investigators proved that HLA identity guaranteed good long term outcome, but unfortunately since there are several thousand HLA genotypes, the possibility of finding an identical kidney for any individual without a genotypically identical sibling was remote.

Throughout this long period of relative scientific stagnation in clinical transplantation the frontier subtly changed to mechanics. The need for multi-institutional programs became

apparent, and several such groups developed. The Midwest Organ Bank and New England Organ Bank are examples. The largest of these was the Southeastern Organ Procurement Foundation (SEOPF) which

SLIDE 5

eventually included some 44 or 45 centers. These groups developed regional recipient lists, computerized matching, and regional cross matching trays. They established standards for recognizing donors, organ retrieval techniques, preservation and transportation. Public education was patronized. These were the nuts and bolts issues, perhaps mundane, but essential matters.

SLIDE 6

In 1983 a new immunosuppressive agent brought real progress. Cyclosporin which is not marrow toxic and does not affect immunologic memory was introduced. It improved renal transplantation but it revolutionized extra renal transplantation. Survival of liver and heart transplants doubled and tripled. Pancreatic and lung transplants became feasible.

SLIDE 7

Monoclonal technology produced OKT3, a kind of purified antithymocyte globulin, which made the treatment of rejection more

reliable.

This increased the demand for transplants immeasurably and experimental procedures became demanded as therapy.

The country seemed shocked to learn that a national system designed to deliver this service was nonexistent. A hue and cry arose and the congress passed a law in response.

This law, the National Transplant Act of 1984 required a National Organ Procurement and Transplantation Network and was an effort to establish a national health care policy in transplantation. This law established transplantation as a scientific clinical discipline by the act of recognition.

The National Transplant Act in itself broke new ground. In the history of these United States when government insured people for certain care, the issue of who delivered the care and where it was delivered was left to the medical profession, but this policy defined who could deliver the care and where. Thus, it was not a blanket insurance but covered only those patients treated under specific guidelines. This principle was established almost unnoticed and generated almost no response. The following series of slides illustrates the current status of clinical whole organ

transplantation.

SLIDE 8

This slide shows the number of transplant centers in the US and associated organizations which belong to UNOS, the national OPTN.

SLIDE 9

There are 278 transplant centers approved by UNOS to transplant the following organs.

SLIDE 10

In the calendar year of 1993 the following transplants were performed: approximately 11,000 kidneys, 3,442 livers, 2,300 hearts. This does not seem too bad for a whole new discipline which came to experimental reality only 32 years ago, but --

SLIDE 11

This is a list of the patients waiting for organs on 1 Feb 1995. A total of 34,008 patients. More than 1/3 of these patients will die waiting for an organ.

What are the challenges?

SLIDE 12

More organs and longer survival. Insofar as survival is concerned,

look at this slide.

SLIDE 13

These are from the UCLA national registry for kidneys. Note the enormous numbers and the log scale. A similar graph can be drawn for the results of liver, heart, or any other organ transplant.

The fact is that almost all progress in long-term survival has been produced by improved survival within the first year. The rate of graft loss after the first year continues unchanged over the last 15, now 20 years.

What does this mean? I think you may take this as a testimony to the strength of the human immune system. Since the origin of man, foreign protein within the body has been bad and commonly leads to death, so we have developed an extraordinary system of isolating and destroying such material. A thirty year effort to subvert this mechanism after several million years of evolution might be expected to be difficult. The body does not forget. As long as an organ of foreign protein is present, the body unceasingly attacks, and although the attack is blunted by drugs or the organ adapts in some way. The relentless attack continues and

eventually the immune system wins and the organ is destroyed.

SLIDE 14

What is needed is a way to convince the body that the new tissue is autogenous so that it will be tolerated as an intrinsic component of that body.

This process is called acquired immunologic tolerance. It can be produced in lower animals by various manipulations. This was shown in the 50's, but a practical way of producing it in the adult human has not been developed. I do believe that will be accomplished if not during my career, then during the next few decades. Our laboratories at LSU have been working with this problem for the past few years. If you are interested, perhaps we can discuss it more in the discussion period.

Such an innovation would stretch the organ supply since one graft would last indefinitely and repeat grafts would not be required. It would obviously greatly decrease morbidity.

Another avenue of research is the use of organs from other animals. There is great interest in this subject at present. The pig seems to be the most promising donor, but I am not too optimistic about this effort. So long as we cannot convince the

body to accept human tissue, it does not seem likely we can convince it to accept pig tissue.

This 33 year odyssey has led to many changes and new disciplines.

The transplant immunobiologist has developed a much clearer understanding of the fundamental function of the immune system. Antigen processing, multiphasic immune responses, self-identification, immune surveillance are a few new concepts generated by this field.

The transplant surgeon, internist, and coordinator are completely new professionals.

General surgery of the liver, kidney, pancreas and other organs has benefitted. Autografts and ex-vivo surgical repairs have become common. So, although the journey is not complete, a great distance has been traveled.

ETHICS

I wish to spend the remainder of my time discussing the impact of transplantation upon our system of ethics. Transplantation has already had an impact in several areas.

SLIDE 15

The identical twin transplant in 1954 was the first time in human history that a healthy person was operated upon for the benefit for another person. Some have termed this modern cannibalism, and it was a major step. Living relative donors are now generally accepted as ethical, and many transplant centers in this country will now accept distant relatives, spouses, or even close friends so long as there seems to be a true emotional attachment and a free choice. This is considered ethical.

In some countries such as India, rich people now buy kidneys from poor people. These operations are being done by respectable professionals in those communities. Could poor people sell vital organs from unwanted children? Where will this stop?

SLIDE 16

Transplantation created a need for organs. It was soon apparent that cardiac cessation as a signpost of death occurred too late. The agonal phase of cardiac death usually led to irreversible damage to other organs. The definition of death had to be changed. A committee at Harvard studied and reported on irreversible coma, and the concept of neurologic death was the consequence. The first report of this concept was in 1968. Within

ten years death pronounced on neurologic criteria was generally accepted in the western world. This was a remarkable event when you consider that for the entire preceding history of man death was diagnosed on cessation of the heart. Yet, it took only a decade to change the marker from heart to brain. While this ultimately reflects the confidence the public has in the medical profession, it may not be the end.

There has already been a national public debate on anencephalic infants. This is an anencephalic infant.

SLIDE 17

SLIDE 18

SLIDE (BLANK) 19

Such babies do not meet the criteria of neurologic death, but all die by 30 days post partum. Many argued, including parents, that the organs should be used immediately for others, but the groups representing right to life won that debate at least temporarily.

The continuing pressure for human organs will force continuing debate on where and how organs are obtained, and there will never be an adequate supply.

In China today organs are said to be harvested from condemned **criminals**. That may be reasonable except that in China and in many other countries of the world we are uncomfortable with what these "criminals" are condemned for. What about hopelessly retarded individuals, what about vegetative patients, the permanently insane? Don't take this matter lightly. When the powerful of the earth need organs, strange things happen. Some two years ago the governor of Pennsylvania needed a new liver and he got one within a week.

Possibly an anencephalic species could be genetically engineered to grow human organs, or perhaps transgenic techniques can humanize pigs.

SLIDE 20

In Elizabethan England there arose a custom that allowed creditors to claim the body of recently deceased debtors which they sold to anatomists to recover some of their money. This pernicious behavior was found illegal by English courts. A judicial precedence developed in English common law which was continued in this country. In effect, this principle held that the cadaver had no property rights. Once dead the remains belonged to the family.

Until transplantation any post mortem use of the cadaver required permission from the next of kin. Thus an individual could not dispose of his own remains.

In the mid 60's a Uniform Anatomic Gift Act was passed which enabled a person to give his/her organs as a legacy. Since then laws have passed requiring a request for organ donation in appropriate situations. Pressure continues to build for extension of the rights of society to claim useful organs from the dead. One such initiative is to establish the principle of presumed consent. In this situation the decedent is presumed to consent for organ donation unless objection has been raised before death. Such legislation seems likely in due course. Already debate is taking place regarding the ethics of paying families of the dead for organs. The circle from Elizabethian time to the present is almost complete. The current argument seeks to re-establish the property value of the cadaver. Society wants that property for the common good, and probably will get it.

These are matters which concern us all, not just scientists. It is clear to me that the possibility of transplantation will continue to cause modification in our ethical systems. Such events

carry within the seeds of destruction of the concept of the sanctity of the individual. This would be a fundamental change with enormous implication.

SLIDE 21

There are said to be four foundation stones upon which civilizations exist. One is a common set of mores and folkways. Without this the civilization cannot continue. There is no center to hold it together. Thus, to abandon the principle that each individual is sacred is not a step to be taken without peril to us all.

But, of course, cynicism is said to be a part of the aging process. Perhaps my concerns are symptoms rather than sound reasoning. Yet, I cannot help but wonder: What hath been wrought by my generation of surgical scientists?